REMARKS

Amendment

Applicants have amended the specification to remove browser-executable codes per the Examiner's request. Applicants further have amended the claims to recite more clearly and distinctly that which they consider to be the inventions, and respectfully submit that all new claims are adequately supported by the specification as originally filed. For example, support for the various linking group new claims 72-85 may be found at page 18, line 13 *et seq.*, and the recitation of a core sequence consisting of 4-11 amino acid residues in Claim 86 is supported by, *inter alia*, Table1 starting on page 32. No issues of new matter are believed to be raised and entry of the amendments and favorable reconsideration are respectfully requested.

Restriction Requirement

The Office Action maintained and made final the restriction requirement as to between alleged Groups I and II. Applicants respectfully traverse and request withdrawal of this requirement.

As an initial matter, for two claims to be properly restricted, they must be (1) independent and distinct, and (2) pose a *serious* burden on the Examiner. See MPEP §803. Applicants respectfully submit that a claim to a monomeric peptide is neither independent from, nor distinct of another claim to a dimeric peptide of the monomeric peptide. Therefore, even under the curious interpretation by the PTO that the phrase "independent and distinct" in 35 U.S.C. §121 means "independent or distinct," a claim to a peptide monomer is NOT restrictable from its corresponding dimer.

According to the MPEP, the term "independent inventions" has the same meaning as "unrelated inventions", and

> [t]he term "independent" (i.e. not dependent) means that there is no disclosed relationship between the two or

> more disclosed subjects disclosed, that is, they are unconnected in design, operation, or effect . . .

MPEP §802.01.

Examples of dependent subjects used in the same section of the MPEP include (1) process and apparatus used in the practice of the process; (2) composition and the process in which the composition is used; and (3) process and the product made by such process.

In contrast, examples used in the 7th Edition of the MPEP for independent subjects are things that are completely unrelated, such as a shoe and a locomotive engine. Accordingly, there is absolutely no basis for the assertion that a peptide monomer and its dimer molecule are unrelated. Therefore, the Office Action clearly is not basing the restriction requirement on the argument that the two type of claims are independent.

By requiring restriction between the two alleged groups, then, the Office Action essentially asserts that claims in these two groups are "distinct."

According to the MPEP, "[t]he term "distinct" means that two or more subjects are . . . PATENTABLE (novel and unobvious) OVER EACH OTHER (though they may each be patentable over the prior art)." MPEP §802.01 (capitalization original).

In other words, the Examiner is asserting that the monomer peptide is patentable over a dimer peptide comprising the monomer. Applicants, however, respectfully disagree, and submit that the two alleged groups are not "distinct" from each other as the term is used in the context for restriction requirement analyses. Consequently, applicants respectfully submit that a restriction requirement between claims in alleged Groups I and II is improper, and these claims should be rejoined and examined on the merits.

The Office Action mentions that examination of both groups may require additional searches. The dimer claims (e.g. claim 14), however, all depend from

the monomer claims (e.g. claim 1 and 12). Accordingly, if the monomer claims are determined to be patentable, the dimer claims are automatically patentable, and no additional search is required. Nevertheless, the MPEP requires that for a proper restriction requirement, *serious* burden *in addition to* the establishment of an "independent or distinct" relationship. See MPEP § 803.01. Because the Office Action failed in establishing any of these elements, the restriction requirement is improper and should be withdrawn.

Objection to Drawings

Applicants will submit formal drawings which will overcome the objections thereto when the claims are indicated to be allowable.

Objections to Claims and Specifications

Applicants have amended claims 12 and 18 such that they no longer depend from cancelled claims. Applicants have also amended the specification to remove browser-executable codes therefrom. Accordingly, it is respectfully submitted that the objections to the claims and to the specification have been overcome.

Claim Rejections Under 35 U.S.C. § 112, ¶ 1

The Office Action rejected all pending claims for alleged lack of enablement under 35 U.S.C. § 112, first paragraph. The Office Action asserts that the claims did not recite specific SEQ ID numbers, or any specific amino acid sequences, that the structural element, "monomeric monocyclic peptide," does not provide sufficient "guidance," and that the specification does not contain enough working examples as to the structure associated with the functional properties. Applicants respectfully traverse, and submit that the specification provides ample working examples of the claimed monomeric monocyclic peptides with the claimed functions.

The Office Action seems to argue that due to the lack of specific amino acid sequences, a large amount of experimentation may be needed to determine which

monocyclic peptide would have the claimed function. However, as stated in MPEP §2164.04,

> The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989).

Applicants respectfully submit that only routine experimentation is required to arrive at the claimed monocyclic peptides, and to test whether they have the requisite biological activities, and that the specification provides a reasonable amount of guidance. Toward this end, some apparently non-working examples are included in the specification to show the ease with which screening experiments are done and that no undue experimentation is involved.

Furthermore, contrary to the assertions in the Office Action, the claimed monocyclic peptides do not encompass an infinite number of peptides. Rather, all of the claimed peptides, as demonstrated by the working examples, are based on the loop fragments of the growth factors VEGF, VEGF-C or VEGF-D.

Because the loops are known to have only a small number of residues, only a very limited amount of screening would be required to identify those that, when cyclized, maintain its affinity with one of the receptors for the growth factors. This amount of experimentation is very reasonable and is not "undue" in the context of enablement analysis under 35 U.S.C. § 112, ¶ 1.

Similarly, the open-ended connector "comprising" in the claims (cf. Office Action, page 7, first full paragraph) does not make the claims less enabled, because no undue experimentation is required to determine how much "additional" sequences a monocyclic peptide may contain to retain its claimed biological functions. In addition, the claimed peptide, be it monomeric or dimeric, does not have to be "more" effective than those retaining the "natural" sequence (cf. Office Action, page 5, third to last line); and no *in vivo* data (cf. Office Action, page 6, lines 21-23 and the sentence bridging pages 6 and 7) is required for a claimed invention (peptides or pharmaceutical compositions) to be enabled. See *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

In order to expedite prosecution, applicants have amended the claims to emphasize that claimed monoccylic peptides comprise a core sequence based on one of the receptor-binding loops 1-3 of VEGF, VEGF-C or VEGF-D, and a linking group at each of the ends that are linked to form the cycle. In view of the above arguments and the amendments, applicants respectfully submit that the lack-of-enablement rejection should be withdrawn.

The Office Action further rejected all pending claims for alleged lack of written description under 35 U.S.C. § 112, first paragraph. The Office Action states that the specification contains only three examples, i.e. SEQ ID NOs: 5, 6 and 7 that have actually been shown to have the claimed biological functions, and thus does not provide an adequate written description of the claimed genus. Applicants respectfully traverse.

Applicants respectfully submit this rejection is improper because the specification describes the subject matter as claimed in such a way as to

reasonably convey to one ordinarily skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus of monocyclic peptides and dimers thereof, and the specification describes numerous representatives of this genus, e.g. Peptides 1, 2 and 3 (corresponding to SEQ ID NOs: 5, 6, and 7) (mononers) and Peptides 4, 5 and 6 (dimers). In addition, the specification describes how variants of the specifically disclosed core sequences can be obtained by an ordinarily skilled person, and further provides guidelines as to which specific amino acid residue of the polypeptide are conserved for maintaining a receptor binding activity. *See* e.g. page 15, lines 30 et seq. of the specification. Furthermore, methods for testing such variants for receptor-binding activity are specifically described, see e.g. Example 4.

As discussed above, the claimed peptides do not have to be more effective than those possessing the native loop sequence as the core sequence. In addition, the claimed genus is not highly variable in view of the fact that the loop sequences are relatively short, are well-characterized, and have highly conserved structural and functional characteristics. Accordingly, applicants respectfully submit that the specification has described sufficient members of the genus, and an ordinarily skilled person would consider that applicants had possession of the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejection Under 35 U.S.C. § 103(a)

The Office Action rejected all pending claims as obvious over Stacker et al. (1999) in view of Potgens et al. (1994), stating that Stacker disclosed "monomeric monocyclic compounds" such as VHD, and Potgens disclosed "monomeric monocyclic peptides" having certain mutations that interferes the biological activities of VEGF. Because the Office Action incorrectly interpreted the disclosure in the two references, applicants respectfully traverse this rejection.

As an initial matter, the instant inventors, through homology based computer modeling and other technologies, obtained the insight that the exposed

loops of the VEGF family of growth factors are critical for the receptor binding activities. Specifically, the inventors examined a model of the three dimensional structure of VEGF-D which was prepared computationally, and compared this model with the experimental model of VEGF. The inventors identified "loops" (i.e. segments of peptide chain that are largely exposed to the solvent and are the parts of the protein chain that stick out from the rest of the protein and bend back around on themselves) which are believed to be important for the ligand-receptor interaction. Based on this insight, the inventors conceived the presently claimed invention of "inactive" yet "receptor-binding" antagonists. Again, for the claimed invention to function as intended, the loop structure needs to be maintained. The instant invention uses the two linking groups for constraining a core sequence, which is based on the native loop sequences, to form a monocyclic peptide, and selects those monocyclic peptides having the requisite β-β carbon atom distances.

Neither Stacker et al., nor Potgens et al. discloses such monocyclic structure in their peptides. In fact, Stacker *et al.* only discloses molecules that mimic or are *more* active than the native growth factors. Potgens *et al.*, failed in their attemps to construct VPF/VEGF antagonists (see p. 32884, right column, 2nd to last paragraph), because the mutants they made are inefficient in competing for receptor binding. Potgens *et al.* failed because they did not know that maintaining the loop-like configuration is important for receptor binding. Stacker *et al.* in no way remedies this deficiency. Accordingly, because the two references, even if combined, do not disclose all claimed elements, applicants respectfully submit that the Office Action failed to establish a *prima facie* case of obviousness, and the obviousness rejection should be withdrawn.

For clarification purpose, applicants further amended claim 1, which additionally recite two linking groups, which are not disclosed nor suggested by either of the two cited references. Therefore, applicants respectfully submit that the claims as amended, are novel and nonobvious and are in condition for allowance.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #1064/48505).

Respectfully submitted,

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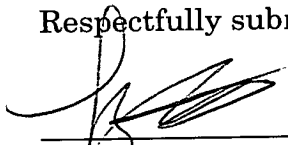

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VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE SPECIFICATION:

The specification has been amended as follows:

The paragraph beginning on page 29, line 21 has been amended as follows:

Initial homology modelling for VEGF-D was carried out using the Swiss-Model automated protein homology server running at the Glaxo Institute for Molecular Biology in Geneva, Switzerland, accessed via the Internet ([http://expasy.hcuge.ch/swissmod/SWISS-MODEL.html;] See Peitsch, 1995). In the C-terminal 23 amino acid residues of the sequences used for modeling there is low homology between VEGF-D and VEGF. Therefore a theoretical hybrid molecule was generated whose N-terminus consists of amino acids Val^{101} - Thr^{173} of VEGF-D (SEQ ID NO:3) and whose C-terminus consists of Gln^{113} - Asp^{135} of $VEGF_{165}$ (SEQ ID NO:4). Thus the C-terminal 23 residues of VEGF-D were replaced with the corresponding residues of VEGF. A homology model of this hybrid molecule was then generated using an X-ray crystal structure of the VEGF dimer (Brookhaven Protein Database reference 2VPF) as a template. The resultant model was transferred to the molecular modelling software Sybyl (Tripos Inc. St. Louis, USA), and the C-terminal residues manually mutated to those found in VEGF-D. The VEGF-D dimer was then minimized (Sybyl forcefield, Powell conjugate gradient minimization, 1000 cycles) to produce the final VEGF-D dimer model, as shown in Figure 1.

IN THE CLAIMS:

Claims 1, 12 and 18 have been amended as follows:

1. (Amended) A monomeric monocyclic peptide which interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, wherein the monomeric monocyclic peptide comprises:

(1) a core sequence which is

(a) a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C or VEGF-D,

(b) a corresponding loop fragment with one or more conservative amino acid substitutions, or

(c) a corresponding loop fragment with one or two amino acid residues deleted or inserted,

(2) a first linking group at one end of the core sequence, and

(3) a second linking group at the other end of the core sequence, wherein the first and second linking groups are connected to form a constraint that cyclizes the peptide such that receptor-binding loops 1, 2 or 3 or the corresponding loop fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D.

12. (Amended) A monomeric, monocyclic peptide produced by [the process of claim 5] a method comprising:

obtaining a receptor-binding loop 1, 2 and 3 of VEGF, VEGF-C and VEGF-D,

modifying the loop with one or more conservative amino acid substitutions to produce a modified loop;

measuring beta-beta carbon separation distances on opposing antiparallel strands of the modified loop;

selecting a modified loop with a beta-beta carbon location with a separation distance of less than 6 angstroms;

providing a linking group in each opposing antiparallel strand at the selected beta-beta carbon location, and

cyclizing the peptide by linking the linking groups to form a constraint that cyclizes the peptide such that receptor-binding loops 1, 2 or 3 or the corresponding loop fragment mimics a respective native conformation.

18. (Amended) A cyclic peptide [produced] according to claim 12, wherein the method [of claim 10] further comprises deleting at least one amino acid residue from said loop fragment prior to cyclizing the peptide[, which] wherein the cyclic peptide interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.